Newborn Screening Quality Assurance Program

2001 TANDEM MASS SPECTROMETRY ANNUAL SUMMARY REPORT

Volume 1 August 2002

INTRODUCTION

The Centers for Disease Control and Prevention (CDC), in partnership with the Association of Public Health Laboratories (APHL), operates the Newborn Screening Quality Assurance Program (NSQAP) to help screening laboratories achieve excellence in technical proficiency and maintain confidence in their performance while processing large volumes of specimens daily. The program produces certified dried-blood-spot (DBS) materials for quality assurance (QA) to improve the scope of services, and to provide immediate consultative assistance when needed. Through interactive efforts the program strives to meet the growing and changing needs of the participants. Tandem Mass Spectrometry is the newest and most comprehensive method for detecting up to 30 disorders. This report is an overview of the specimen preparation and reported results for the 2001 pilot Tandem Mass Spectrometry Proficiency Testing (PT) Program. Comments and suggestions on how we may better serve the newborn screening laboratories are always welcomed.

Newborn screening for detection of treatable, inherited metabolic diseases is a major public health responsibility consisting of six parts: education, screening, follow-up, diagnosis, management, and treatment. Effective screening of newborns using DBS specimens collected at birth, combined with follow-up diagnostic studies and treatment, helps prevent mental retardation and premature death. These blood specimens are routinely collected from more than 95% of all newborns in the United States. State public health laboratories or their associated laboratories screen DBS specimens for inborn errors of metabolism and other disorders that require intervention.

For more than 24 years, CDC and APHL have conducted research on materials development and assisted laboratories with both QC and PT issues. The QA services primarily support state laboratories performing newborn screening; however, privately owned and foreign laboratories can also be accepted into the voluntary program. Currently, the program provides QA services in the form of quarterly PT panels that include amino acids and acylcarnitines. Quality Control materials are available for amino acids, however, we do not provide QC-DBS materials for acylcarnitines at this time. Dried-blood-spot materials for QC and PT are certified for homogeneity, accuracy, stability, and performance for most methods.

Along with the quarterly PT panels, which use blind-coded DBS specimens, the PT program provides to each laboratory an independent external assessment report of its performance. PT specimen panels are shipped to the laboratories in January, April, July, and October of each year. The laboratories have a one-month deadline for submitting the data. A quarterly summary that reports the enrichment values along with a summary of participant means and cutoffs is compiled and returned to the participating laboratories. At the end of every year, the program publishes an annual report to summarize the data from four quarters and to serve as a resource of accumulated information that could benefit all laboratories involved in newborn screening efforts.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention (CDC)
and the
Association of Public Health Laboratories

TANDEM MASS SPECTROMETRY PROFICIENCY TESTING

In 2001, NSQAP operated a pilot PT program for laboratories testing newborn screening DBS specimens by tandem mass spectrometry (MS/MS). Disorders for which these laboratories use MS/MS to test include amino acid metabolic disorders, urea cycle disorders, fatty acid oxidation disorders, and organic acid metabolic disorders. During the year, the program distributed three five-specimen panels to 44 active participants in the MS/MS PT program. Of these 44 participants, 20 were domestic laboratories in 16 states of the United States (Figure 1), and 24 were foreign laboratories in 14 countries

FIGURE 1. Twenty laboratories in sixteen U.S. states participated in the NSQAP tandem mass spectrometry pilot PT program in 2001.

(Figure 2) around the world. This report summarizes the outcome for amino acids and acylcarnitines data collected in 2001 (Figures 9-18). These data, including the first two

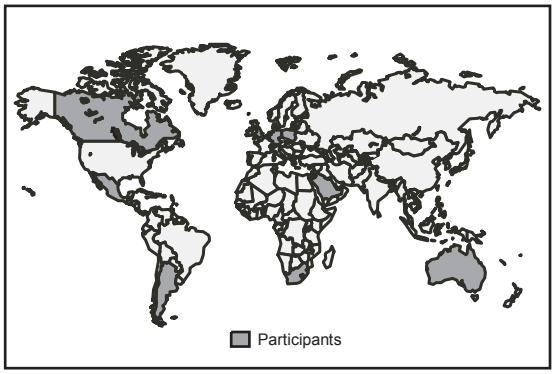
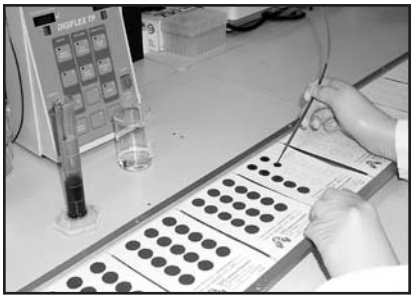


FIGURE 2. Twenty-four laboratories in fourteen foreign countries participated in the NSQAP tandem mass spectrometry pilot PT program in 2001.

specimen panels of 2002, will be used to help establish appropriate cutoff values and presumptive classifications for grading purposes since a grading system is required for PT. Establishment of cutoff values and presumptive classifications will promote the MS/MS component from a pilot status to a PT evaluation status. Because of increasing interest in the DBS MS/MS technology for newborn screening, the participant numbers are expected to increase significantly. The goal is to have the MS/MS PT program in full swing by the beginning of the year 2003.[1]

SPECIMEN PREPARATION

The amino acids PT panels distributed to participants in the 2001 pilot PT program were made up of specimens derived from two sources: blood with a 55% hematocrit of lysed red cells, and the Amino Reference Materials that were prepared from blood with a 55% hematocrit of intact red cells. The PT panels were made using blood from donors with natural endogenous levels or using purified analyte at predetermined levels. Amino acids PT specimens were dispensed on S&S Grade 903 Lot W941 filter paper and the acylcarnitines PT specimens were dispensed on S&S Grade 903 Lot W961 filter paper (Figure 3). The specimen sets or panels were made up of five blind-coded 100 µL DBS specimens that were packaged in zip-closed metallized plastic bags along with desiccant, instructions for analysis, and data-report forms (Figure 4).



Quarterly reports were prepared by the program administrators and distributed to all participant laboratories using results that had been received by the deadline date. Late-results data were not used in the quarterly calculations; however, the late data were included in the statistics of the annual MS/MS report.

This report is the first MS/MS annual report that summarizes the quantitative data from the quarterly MS/MS PT data that were submitted during 2001. Figures 9-18 show the individual lab data in reference to a mean cutoff that was calculated from domestic and foreign laboratory cutoff values submitted for the Quarter 4, 2001, PT panel.

DOSE RESPONSE LINEARITY OF THE AMINO ACID REFEENCE MATERIALS

In 1999, NSQAP produced a six-pool set of multianalyte dried-blood-spot amino acid reference materials (AARMs) as a first step towards standardization of newborn aminoacidopathy screening. The AARMs were certified using isotope-dilution mass spectrometry (IDMS) to validate amino acid accuracy, characterize homogeneity, and check stability in storage.[2] Four of the six AARM reference pools were used as blinded specimens in the first quarterly MS/MS pilot PT panel of April 2001 to determine dose-response linearity among domestic and foreign participants.

Figures 5a-5e summarize participants' analytical results for the AARMs. The target concentrations of these specimens, shown on the X-axes, are equal to the enriched concentration plus the endogenous concentration. The endogenous concentrations were determined by plotting the ion abundance ratios using IDMS for each amino acid versus the amino acid enrichments of the AARM pools and using weighted linear regression analyses of the resulting plots to determine the Y-intercept for each analyte.[2] The Y-intercepts determined from the phenylalanine (Phe), methionine (Met), tyrosine (Tyr), and valine (Val) regression analyses were equivalent to the endogenous concentrations of the blood batch from which the AARMs were prepared. Because the total leucine (Leu) intercept determined by mass spectrometry represented leucine + isoleucine (Ile), high-performance liquid chromatography (HPLC) was used to measure the Leu and Ile fractions of the nonenriched AARM pools. The endogenous Leu concentration, determined by IDMS was derived by multiplying the Y-intercept by the Leu fraction

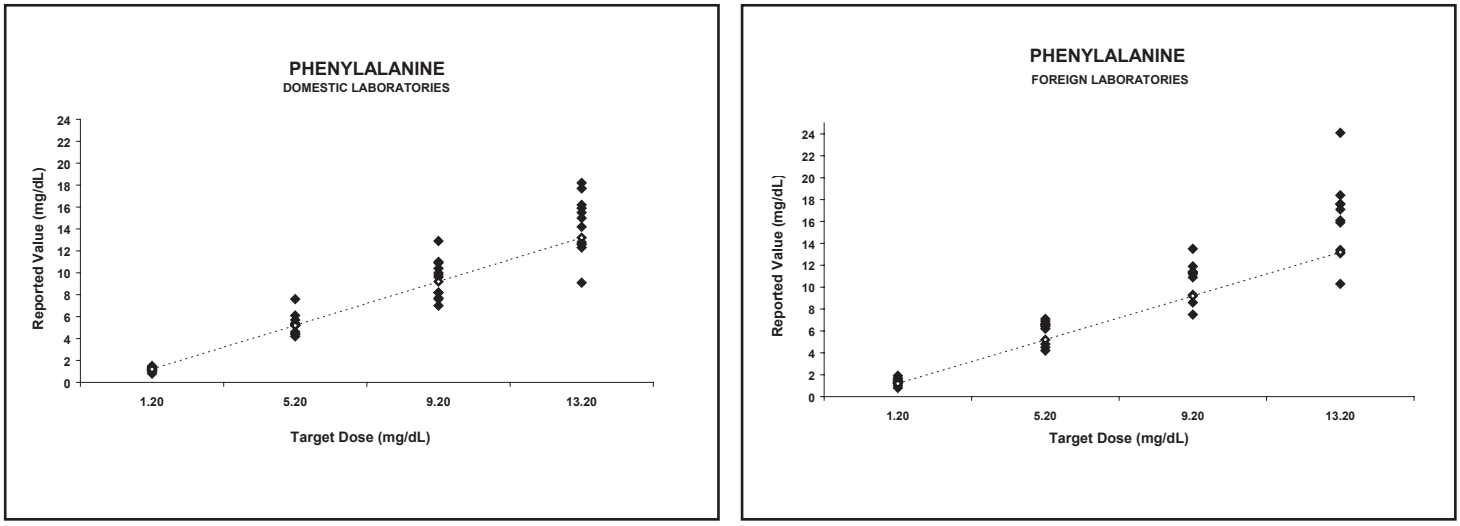


Figure 5a. Phenylalanine AARMs Dose-Response Curves for Domestic and Foreign Laboratories

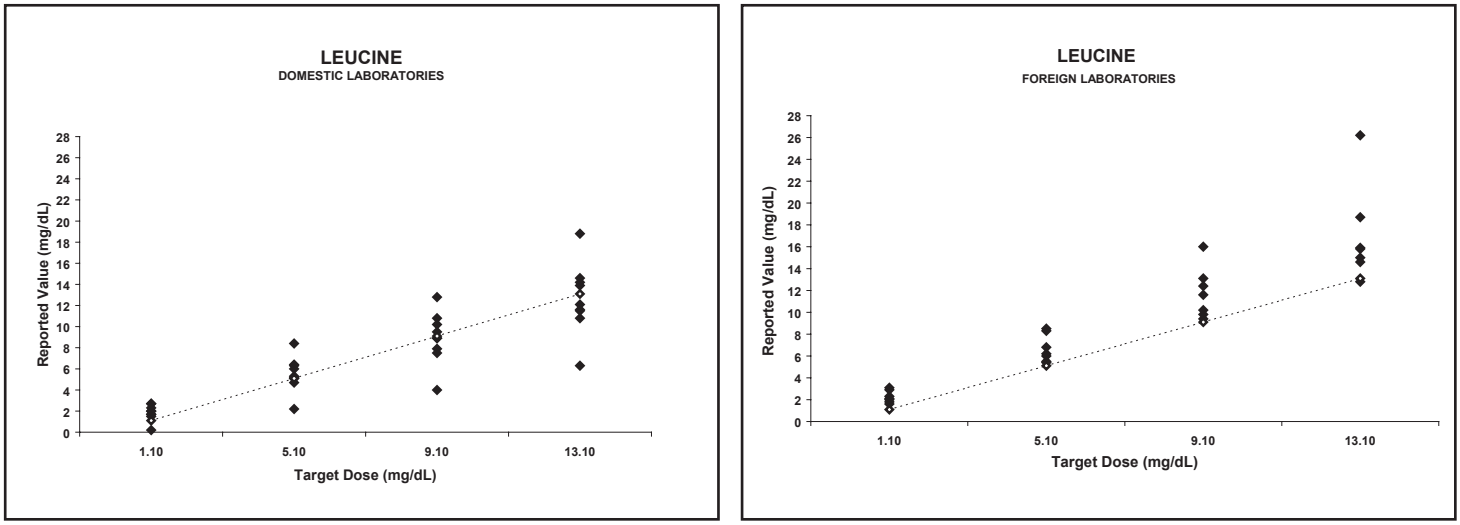
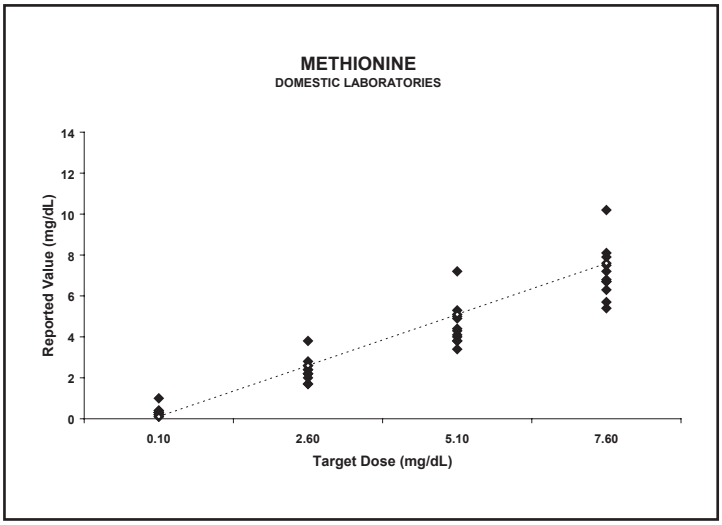


Figure 5b. Leucine AARMs Dose-Response Curves for Domestic and Foreign Laboratories



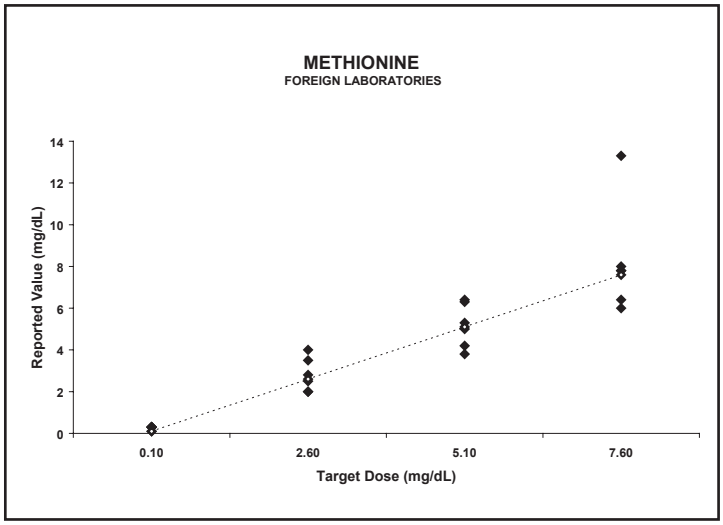
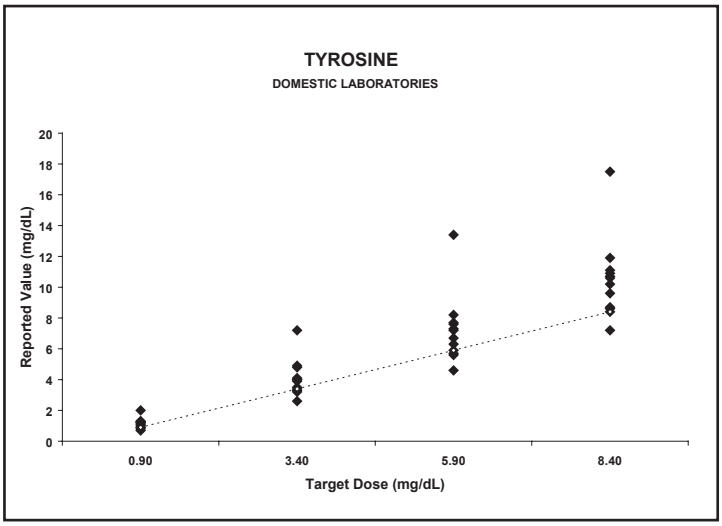


Figure 5c. Methionine AARMs Dose-Response Curves for Domestic and Foreign Laboratories



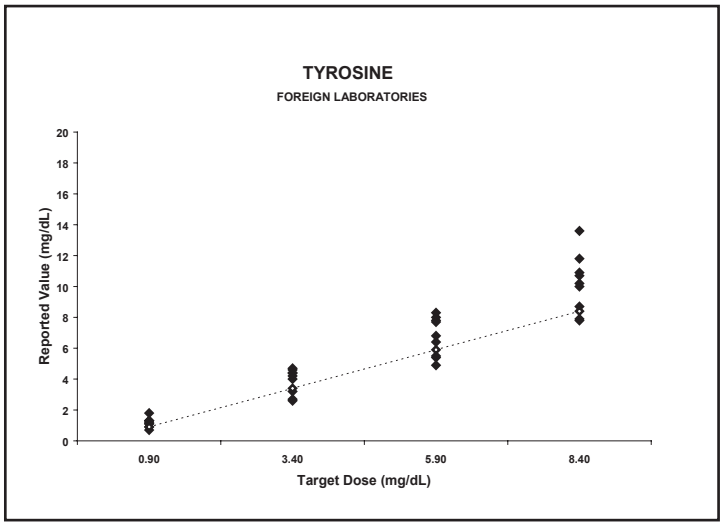
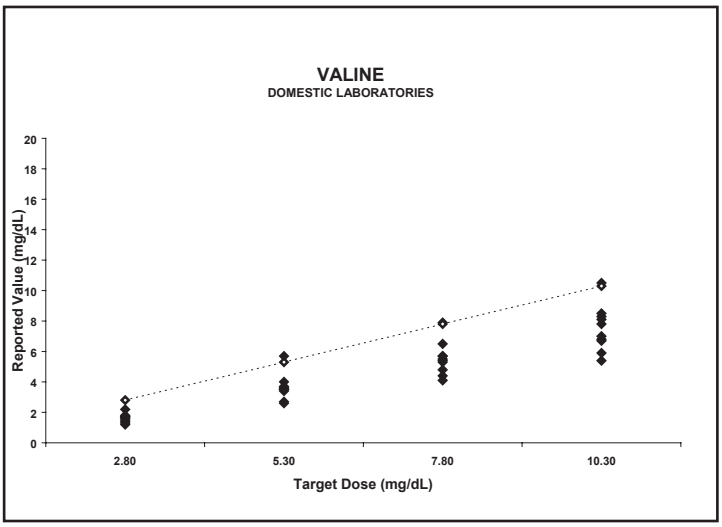


Figure 5d. Tyrosine AARMs Dose-Response Curves for Domestic and Foreign Laboratories



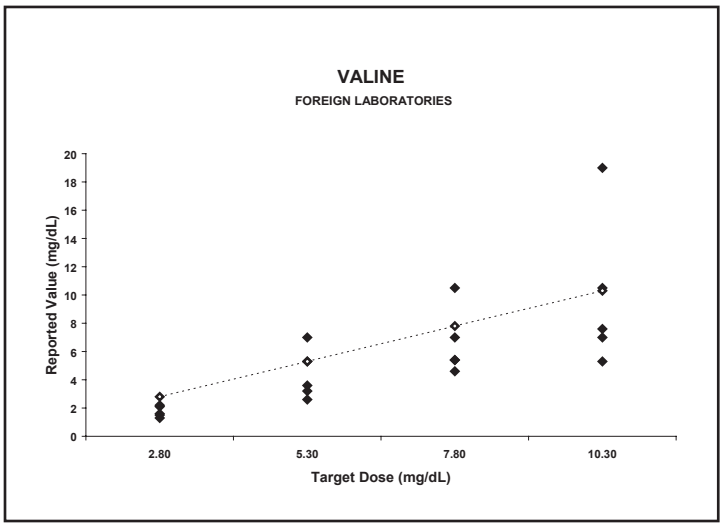


Figure 5e. Valine AARMs Dose-Response Curves for Domestic and Foreign Laboratories

that was determined by HPLC.[2] The reported Phe results for the AARMs were in good agreement with the target values. International participants reported results for Leu that were somewhat above the target value and that may, in part, have reflected participants' methods of calculation and reporting. Since the Leu target value does not include Ile, participants who report Leu + Ile would be expected to submit results with a small fixed high bias. Domestic laboratory results for Met trended lower than expected whereas domestic and foreign laboratory results for Tyr trended higher than expected. Both domestic and foreign results for Val were lower than expected. This outcome was surprising, because the extensive studies carried out as part of the AARMs validation process predicted Val stability equivalent to that of Phe, Leu, and Tyr and more stable than Met.

REPRODUCIBILITY

Periodically, the NSQAP will provide a panel that includes a duplicate specimen in the same shipment or in consecutive shipments to check reproducibility within runs or between shipments. Extensive efforts and continuous checks are made to secure the stability of the DBS materials during storage and shipment. We find that reproducibility checks add reliability to the list of certifying requirements for the quality of our DBSs. The following charts demonstrate the mean reproducibility of Pool A (low enrichment) and Pool B (high enrichment) between two quarters for both amino acids and acylcarnitines.

Figures 6a–6d show participant results from two consecutive distributions of DBS pools. In each group, Pool A represents a low-enriched pool and Pool B represents a high-enriched pool. Results for domestic and

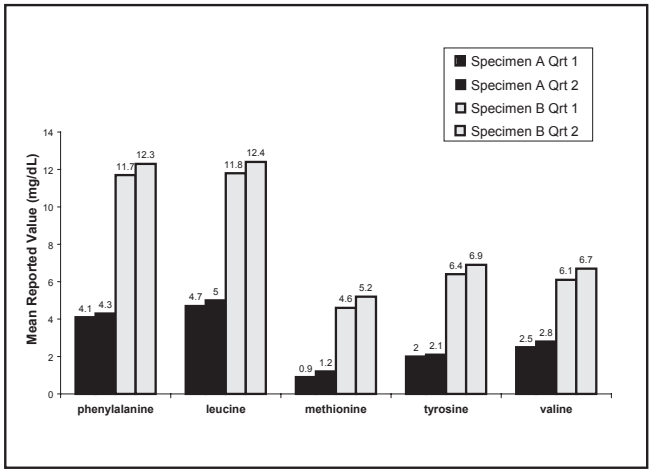


FIGURE 6a. Amino Acids: Mean Reproducibility of Pool A and Pool B Between Quarters Among Domestic Laboratories by MS/MS

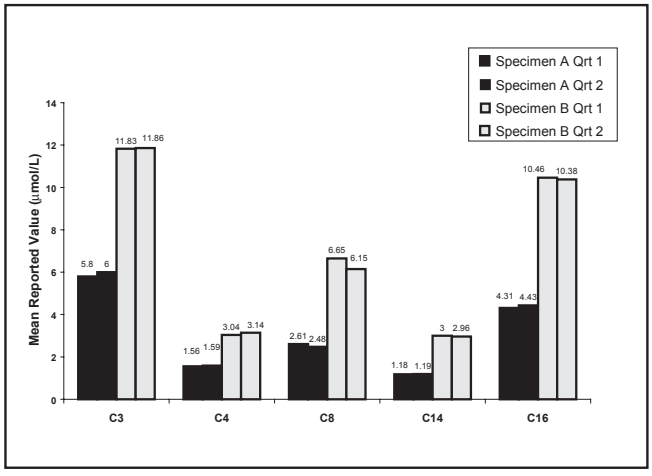


FIGURE 6b. Acylcarnitines : Mean Reproducibility of Pool A and Pool B Between Quarters Among Domestic Laboratories by MS/MS

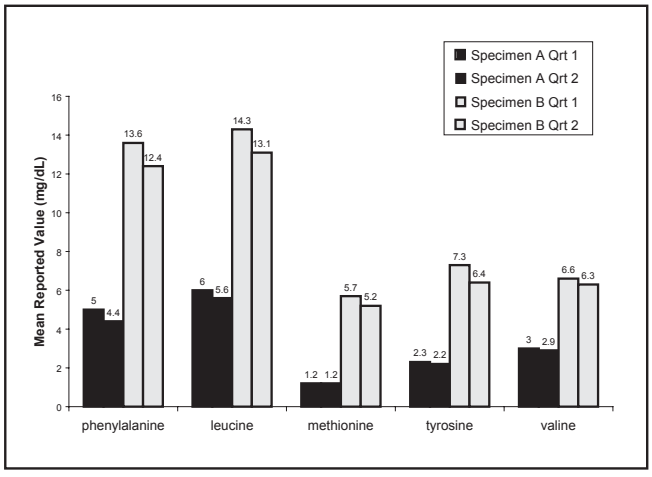


FIGURE 6c. Amino Acids: Mean Reproducibility of Pool A and Pool B Between Quarters Among Foreign Laboratories by MS/MS

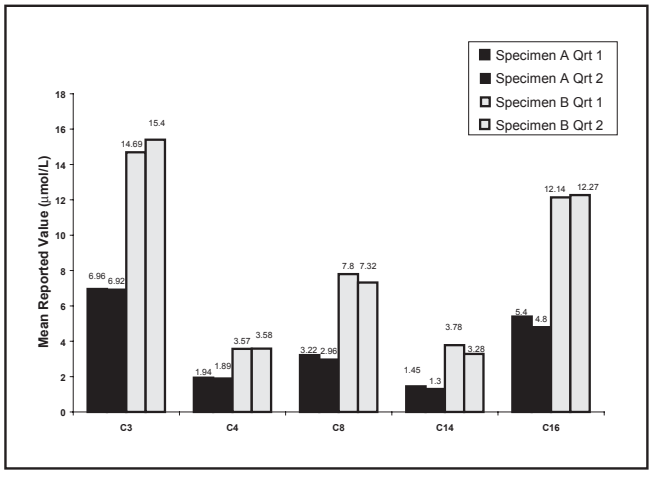


FIGURE 6d. Acylcarnitines: Mean Reproducibility of Pool A and Pool B Between Quarters Among Foreign Laboratories by MS/MS

foreign laboratories are shown because reported concentrations of values from foreign laboratories were higher than those from domestic laboratories. Amino acid results from the second distribution show increases in the mean concentration due to a higher response in the foreign laboratories. The harmonization of amino acid results in the second survey reduced or eliminated the differences between the mean concentrations reported by domestic and foreign laboratories. For the acylcarnitines, between-quarter reproducibility of results was good within both the domestic laboratory group and the foreign laboratory group; however, results from the second distribution of the acylcarnintine pools showed no trend toward harmonization of domestic and foreign reports.

DETERMINATION OF APPROPRIATE CUTOFF VALUES

As part of each PT analyte report, participants are asked to provide their cutoff value. The cutoff value is defined as the first decision level for sorting test results that are reported as presumptive positive (outside limits) from results reported as negative (within limits).

The cutoff values shown in Figures 7a-7e illustrate the distribution of reported amino acid cutoffs for all participating laboratories. The cutoff values shown in Figures 8a-8e illustrate the distribution of reported acylcarnitine cutoffs for all participating laboratories. The values for the mean cutoff are shown for each analyte and were calculated from the cutoff values submitted on the data report form from Quarter 4, 2001.

Most laboratories reported results for all five amino acids, but the number of reported cutoff values varied, with 24 laboratories reporting Phe cutoff values (the largest group) and only 10 laboratories reporting Val cutoffs (the smallest group). The number of laboratories reporting acylarnitine cutoff values ranged from 15 laboratories reporting C16 to 20 laboratories reporting C8 cutoffs. Even if extreme outliers are excluded, the distributions of cutoff values for amino acids and acylcarnitines included in this report show substantial scatter around the means. The cutoff values may vary because of differences in newborn screening practices such as the age of neonates when the screening specimen is taken, because of differences in instrument calibration, and most

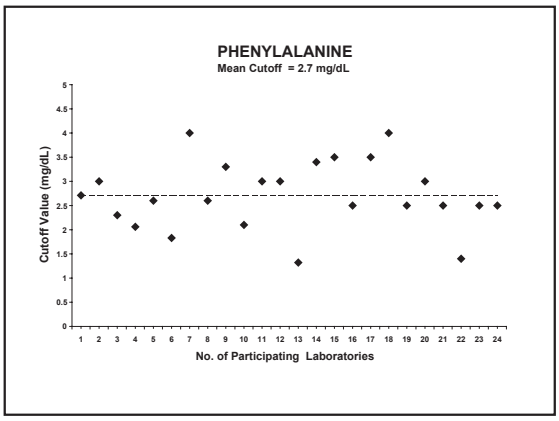


Figure 7a. Reported Cutoff vs. Calculated Mean Cutoff Value for Amino Acids (mg/dL)

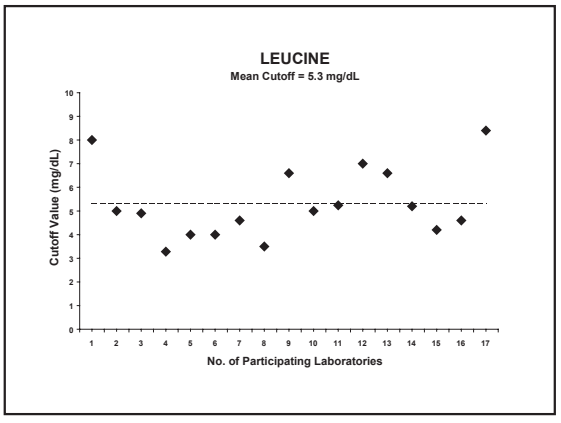


Figure 7b. Reported Cutoff vs. Calculated Mean Cutoff Value for Amino Acids (mg/dL)

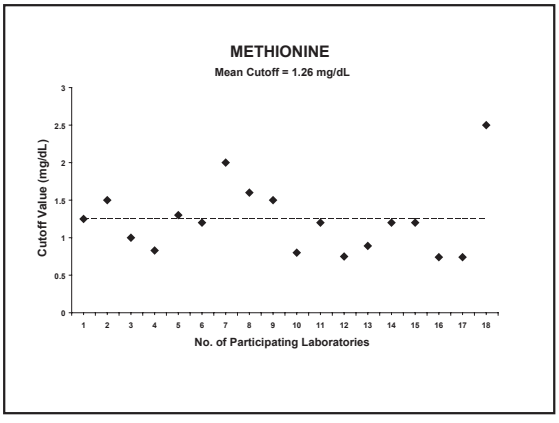


Figure 7c. Reported Cutoff vs. Calculated Mean Cutoff Value for Amino Acids (mg/dL)

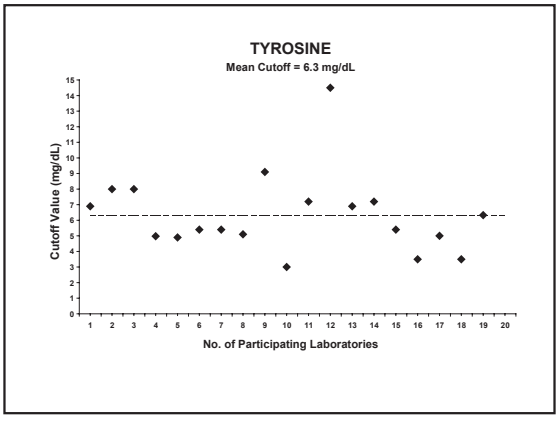


Figure 7d. Reported Cutoff vs. Calculated Mean Cutoff Value for Amino Acids (mg/dL)

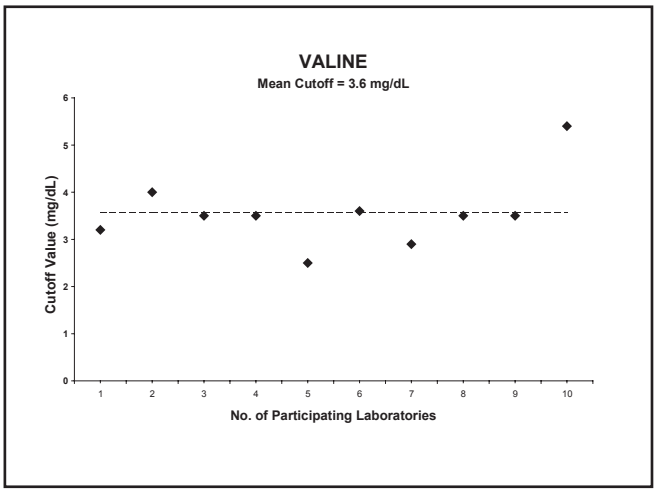


Figure 7e. Reported Cutoff vs. Calculated Mean Cutoff Value for Amino Acids (mg/dL)

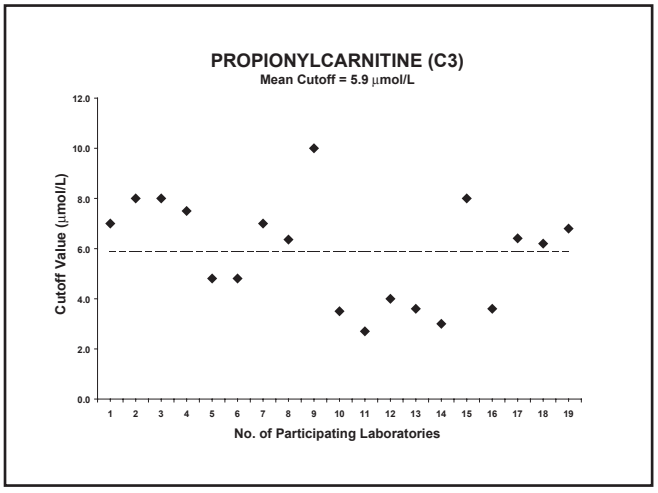


Figure 8a. Reported Cutoff vs. Calculated Mean Cutoff Value for Acylcarnitines (μmol/L)

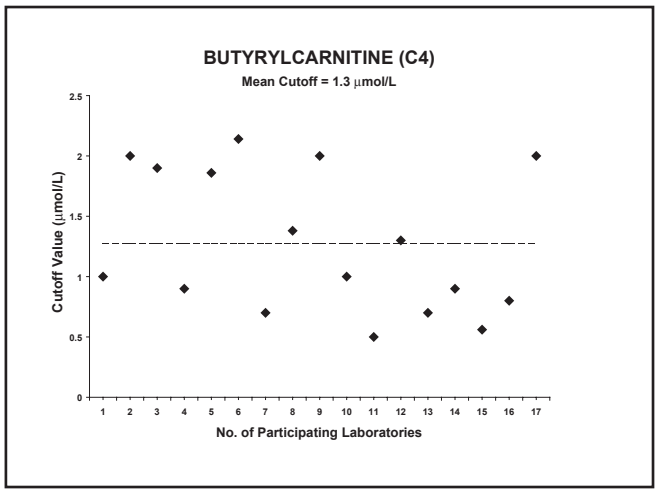


Figure 8b. Reported Cutoff vs. Calculated Mean Cutoff Value for Acylcarnitines (μmol/L)

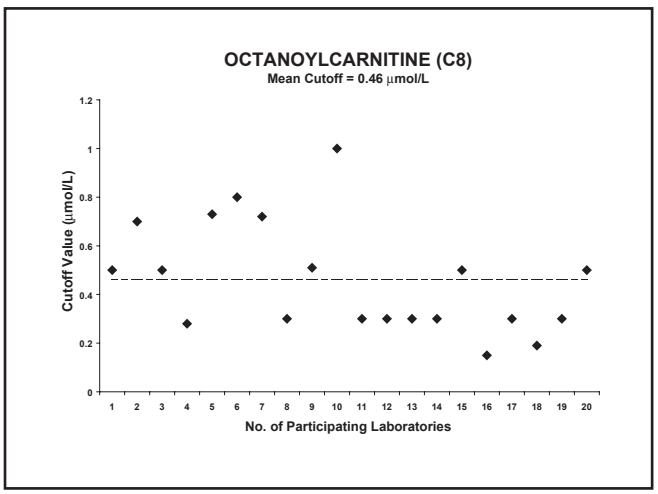


Figure 8c. Reported Cutoff vs. Calculated Mean Cutoff Value for Acylcarnitines (μmol/L)

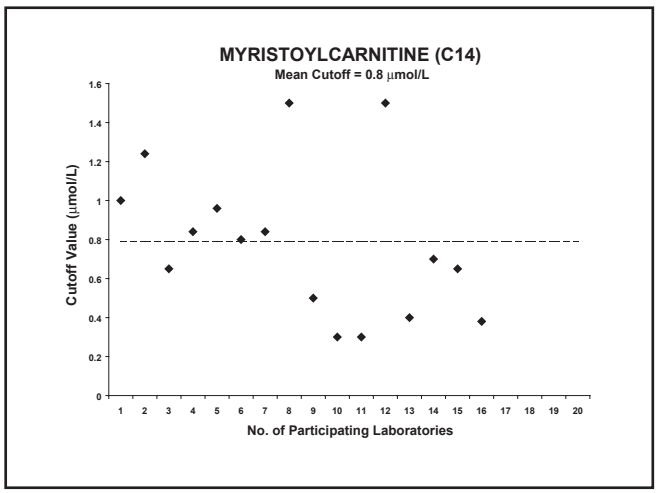


Figure 8d. Reported Cutoff vs. Calculated Mean Cutoff Value for Acylcarnitines (μmol/L)

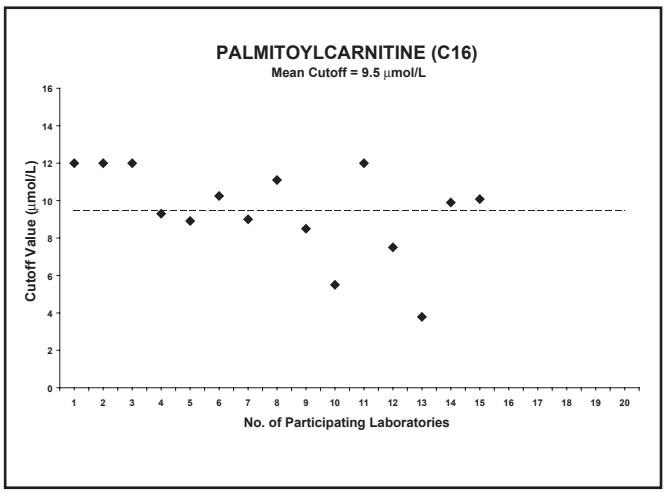


Figure 8e. Reported Cutoff vs. Calculated Mean Cutoff Value for Acylcarnitines (μmol/L)

commonly, due to differences in extraction methodologies (derivatized vs. nonderivatized).

For example, laboratories that do not derivatize amino acid samples before analysis may have lower quantitative values and adjust their cutoff values accordingly. As the MS/MS PT Program expands from quantitative assessment of specimens to include qualitative (presumptive clinical) assessments, the NSQAP will apply the laboratory-reported specific cutoff values, when available, to our judgment algorithm for clinical assessments; otherwise, we will use the NSQAP-assigned working cutoff values that are based on the national mean value for this assessment.

PARTICIPANT RESULTS FOR AMINO ACIDS AND ACYLCARNITINES

The following graphics (Figures 9-18) illustrate the assayed values submitted for each analyte by participant laboratories, domestic and foreign. The dotted line represents the mean cutoff for each analyte determined from Quarter 4, 2001, data report forms (See section on determining appropriate cutoffs). The assayed values were plotted against the overall mean cutoff. The values for the zero nonenriched specimens show the measured endogeneous concentration for the analyte. Variation among data values is influenced by inherent characteristics of DBS testing, by varied differences in extraction methods, and by instrument calibration materials. The standardization of preanalytic derivatization and the use of common certified instrument calibrators will improve precision. Specific procedural inquiries will be added to the NSQAP data-report forms as a means of collecting information that will enable sorting of the data by extraction method, derivatization, and calibration material.

Participant results for amino acids and acylcarnitines showed that reported Phe values, compared with the mean cutoff for Phe, were in good agreement with regard to classification. The nonenriched specimen contained Phe in the normal concentration range, whereas all enriched specimens contained Phe in the abnormal concentration range. Reported Leu concentrations for the nonenriched Leu specimen were clearly within normal limits, and results from the specimen enriched with 11 mg Leu/dL of blood were clearly abnormal. With very few exceptions, participants' results from Leu specimens enriched with 3 mg/dL of blood were classified as normal, and those from the specimen enriched with 7 mg/dL of blood were classified as abnormal. However, results from the Leu specimens enriched with >3 and <7 mg Leu/dL of blood suggest that quantitative results would be scattered above and below the mean cutoff value.

The pattern of Met results was similar to that of Leu. The non-enriched specimen concentrations fell clearly within the normal range; the reported concentrations from the specimen with the highest Met enrichment were clearly in the abnormal range; and the reported concentrations from the specimens with intermediate enrichments suggest that results from Met specimens enriched with >1 mg/dL but <3 mg/dL of blood would be scattered above and below the mean cutoff value for Met. Tyr results for specimens enriched with 0 to 3 mg Tyr/dL of blood fell below the mean cutoff for Tyr, whereas results for the Tyr specimen enriched with 6 mg Tyr/dL blood were scattered around the mean cutoff value of 5.9 mg/dL; thus, no clearly abnormal Tyr specimen was presented in this survey. Participants' reported values for the non-enriched Val specimen and the specimens enriched with 1 mg Val/dL of blood were within the normal range. Five of 22 Val values for the specimen enriched with 3 mg Val/dL of blood were above the mean cutoff value but 7 of 22 Val values for the specimen enriched with 6 mg Val/dL of blood were below the mean cutoff value of 5.2 mg Val/dL, suggesting that results from specimens enriched with > 3 to < 6 mg Val/dL of blood would be scattered above and below the mean cutoff value.

Acylcarnitine results showed that all quantitative values reported for the non-enriched C3 specimen were below the mean cutoff; all reported values for the C3 specimen enriched with 9 µmol/L of blood were above the mean cutoff; and the ranges of quantitative values from specimens enriched with 3 and 6 µmol/L showed some overlap, with 12 of 31 values from the specimen enriched with 3 µmol/L falling above the mean cutoff and few values from the specimen enriched with 6 µmol/L falling below the mean cutoff. For C4, C8, and C14, participants' reported values for all enriched specimens were above the mean cutoff values, strongly suggesting that the NSQAP should reevaluate its enrichment scheme for these analytes. All reported values from the C16 non-enriched specimen and the specimen enriched with 3 µmol/L were below the mean cutoff, whereas reported values from specimens enriched with 6 and 9 µmol/L were scattered around the mean cutoff of 9.5 µmol/L, indicating a degree of overlap in the ranges of quantitative values reported for these specimens.

As the PT program for tandem mass spectrometry measurements expands to include qualitative (clinical) assessments of specimens, cutoff values will play an important role in the evaluation process as well as being used by NSQAP to guide analyte enrichment levels of the PT specimens.

Figures 9a-9e. Participant Results vs. Reported Cutoff Mean Values for Phenylalanine

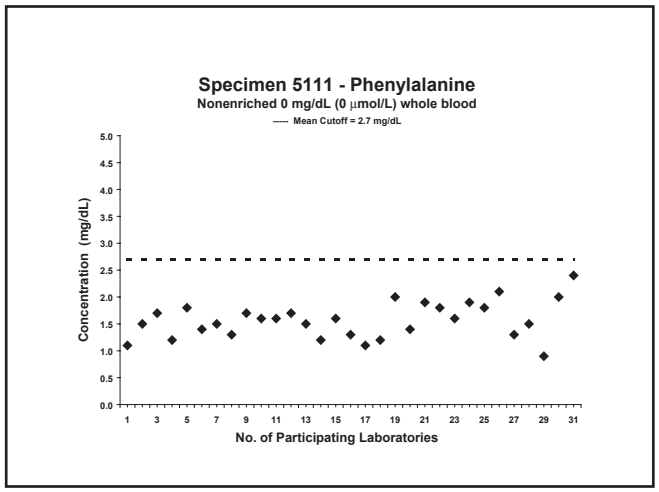


Figure 9a.

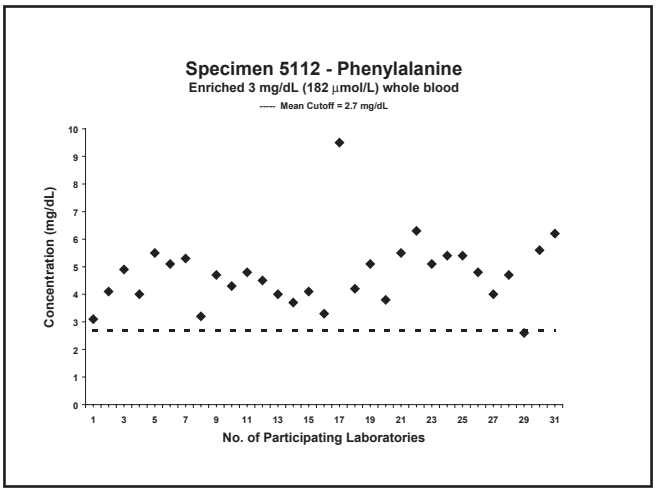


Figure 9b.

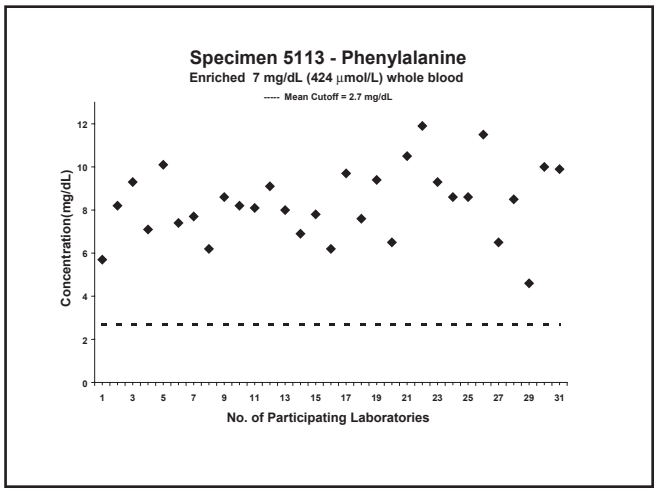


Figure 9c.

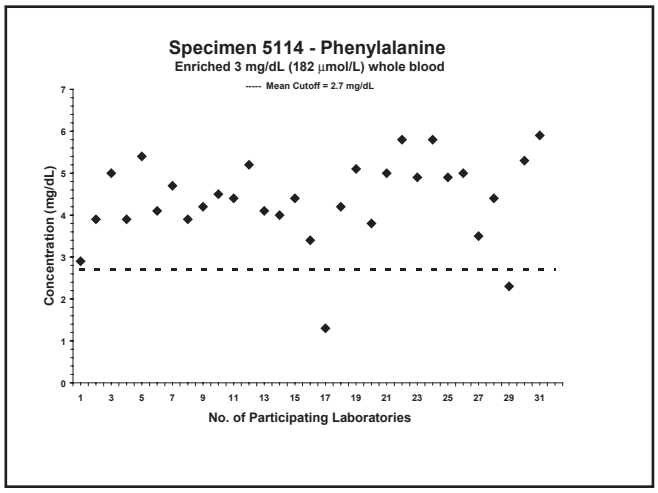


Figure 9d.

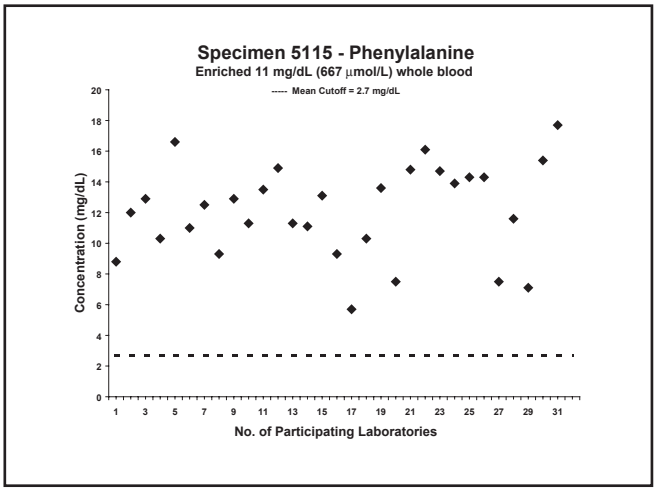


Figure 9e.

Figures 10a-10e. Participant Results vs. Reported Cutoff Mean Values for Leucine

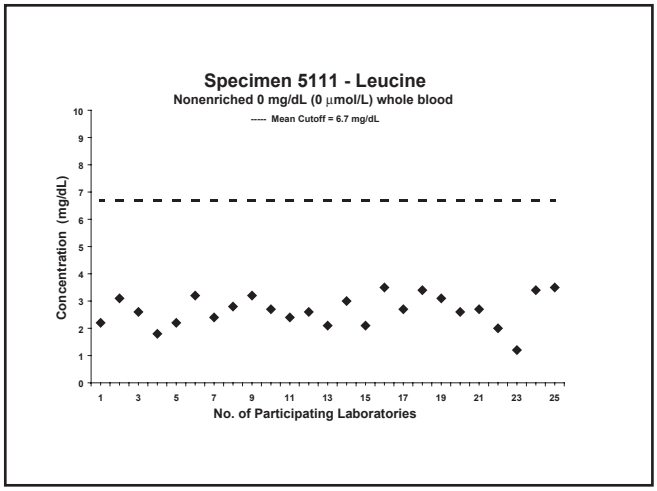
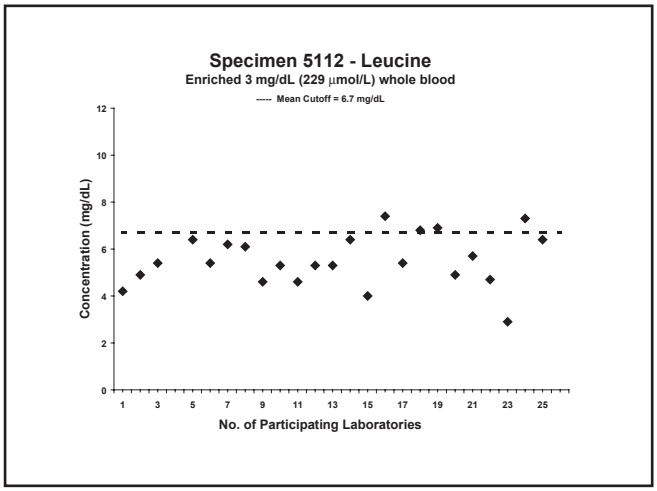


Figure 10a.



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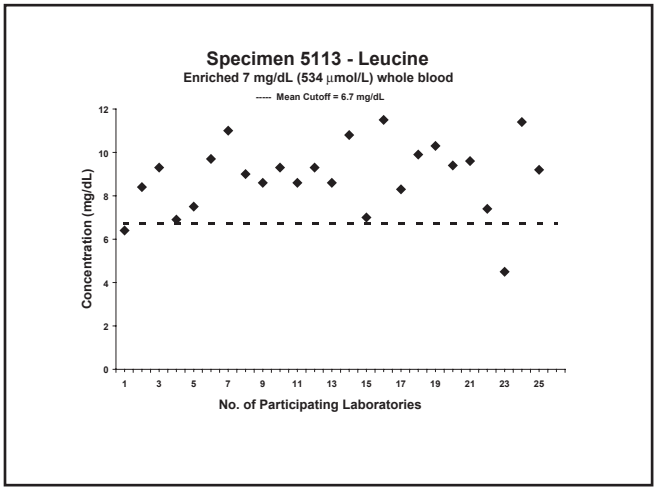

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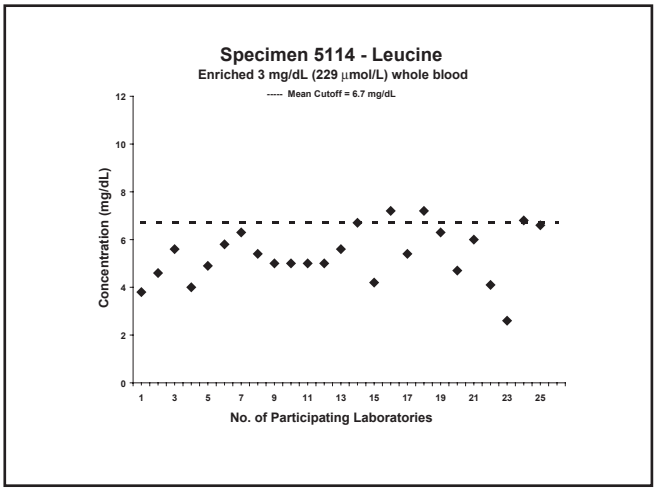

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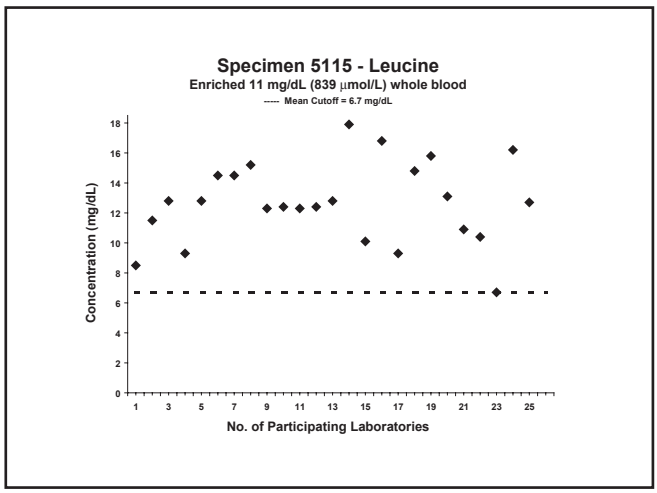
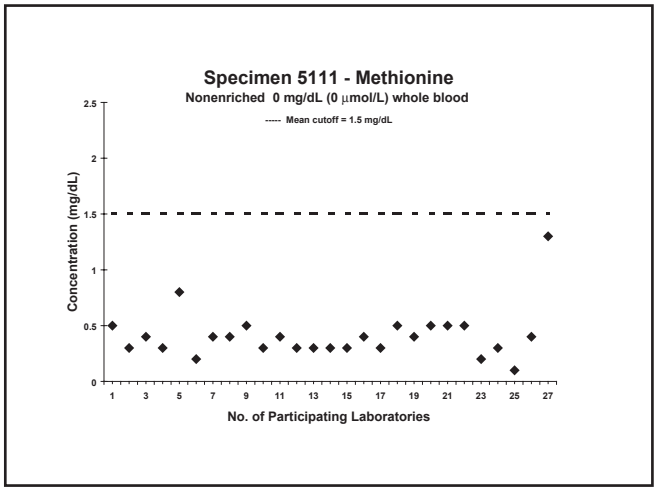


Figure 10e.

Figures 11a-11e. Participant Results vs. Reported Cutoff Mean Values for Methionine



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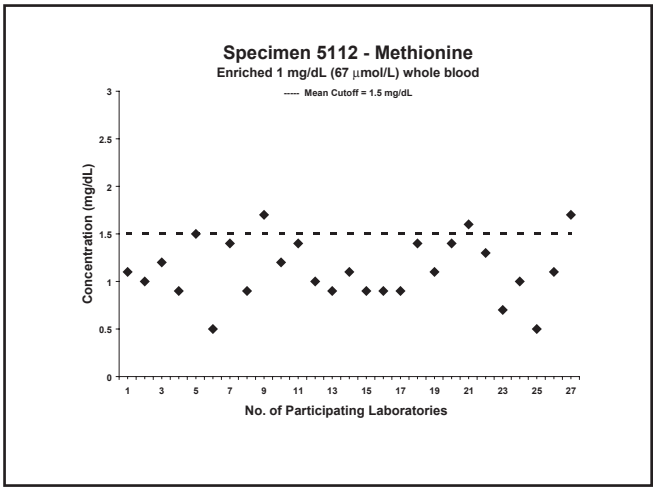

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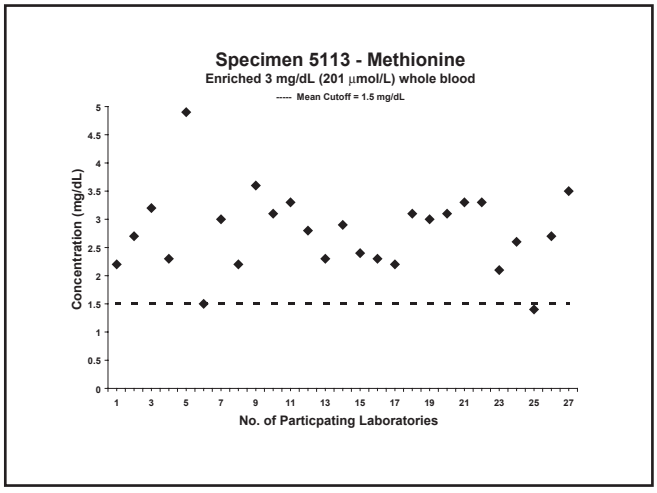

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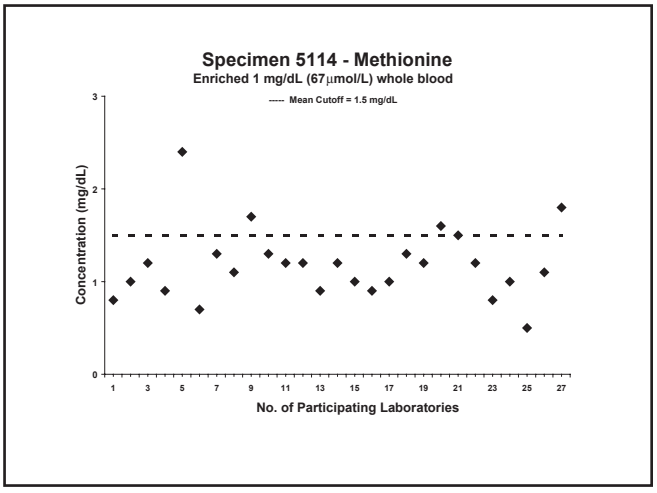

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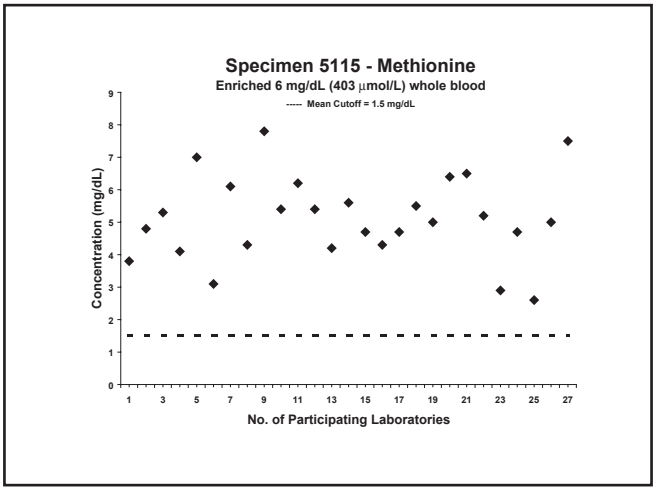
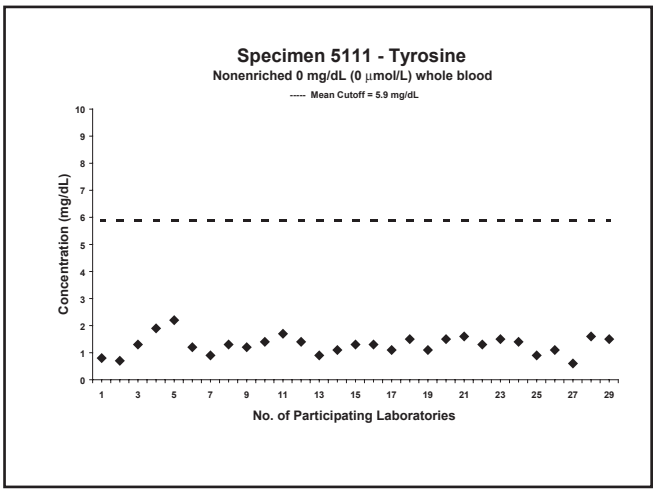


Figure 11e.

Figures 12a-12e. Participant Results vs. Reported Cutoff Mean Values for Tyrosine



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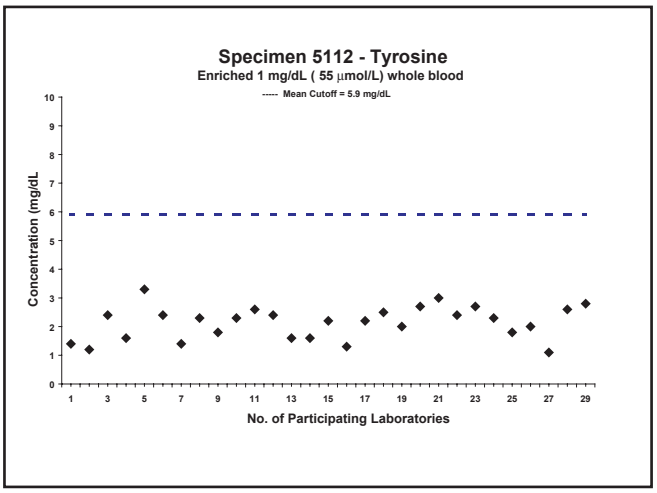
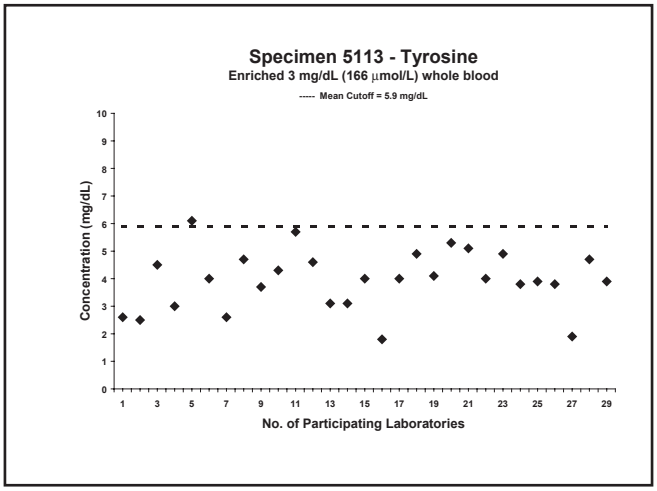


Figure 12b.



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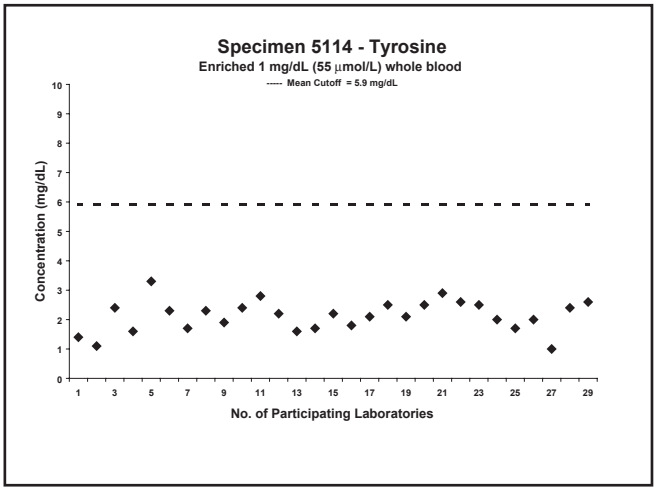

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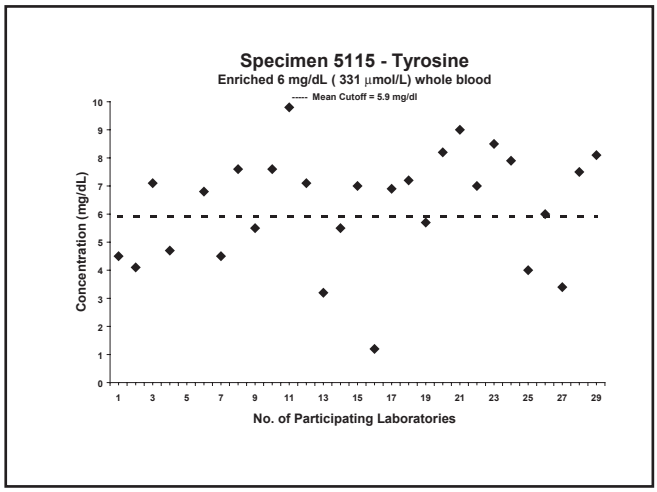
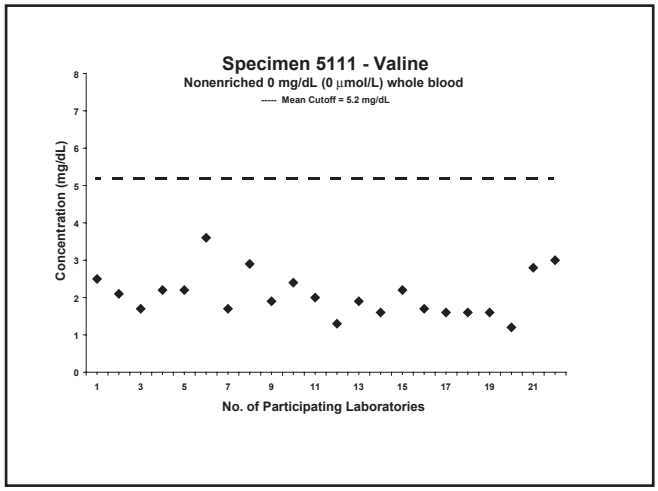


Figure 12e.

Figures 13a-13e. Participant Results vs. Reported Cutoff Mean Values for Valine



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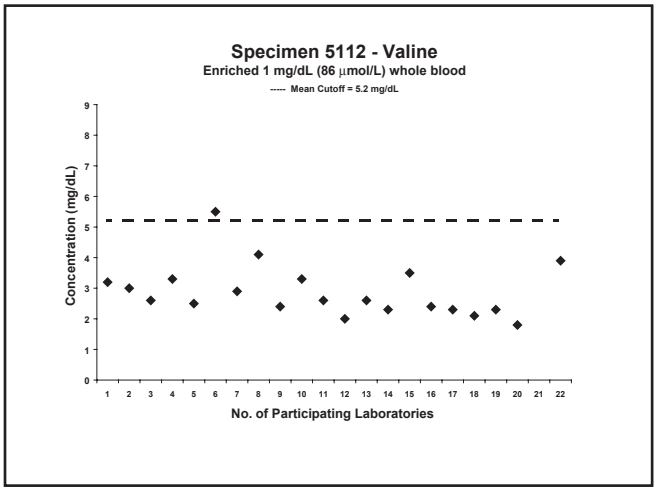
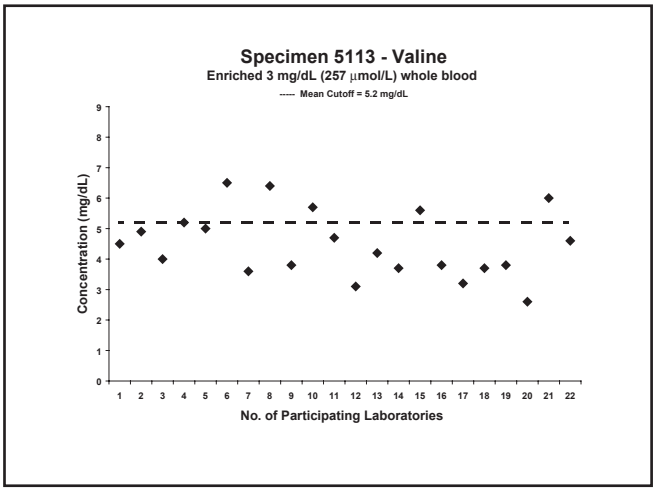


Figure 13b.



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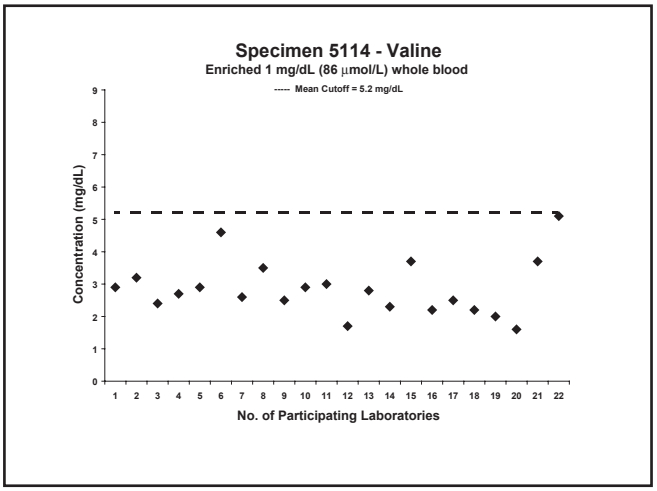

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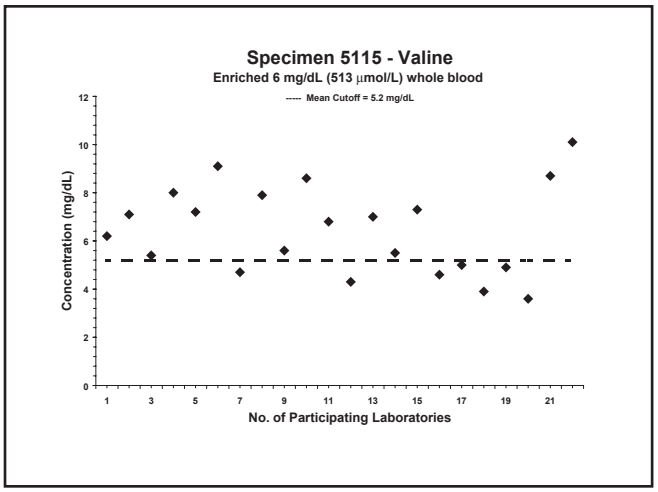
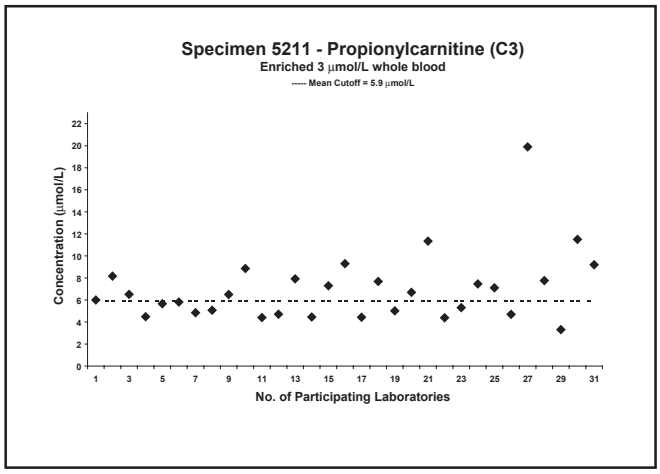


Figure 13e.

Figures 14a-14e. Participant Results vs. Reported Cutoff Mean Values for Propionylcarnitine (C3)



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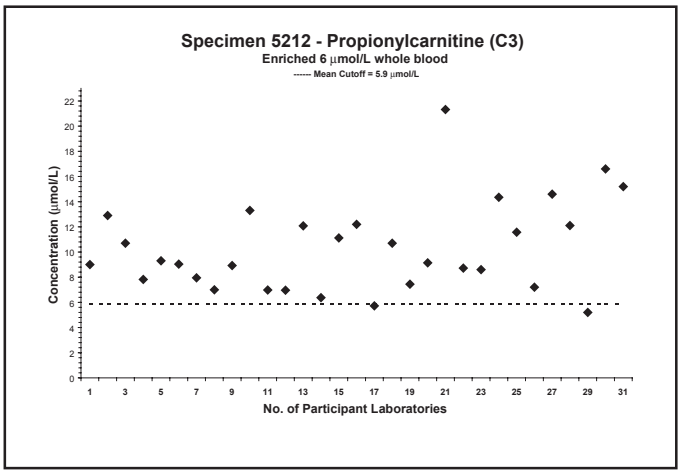

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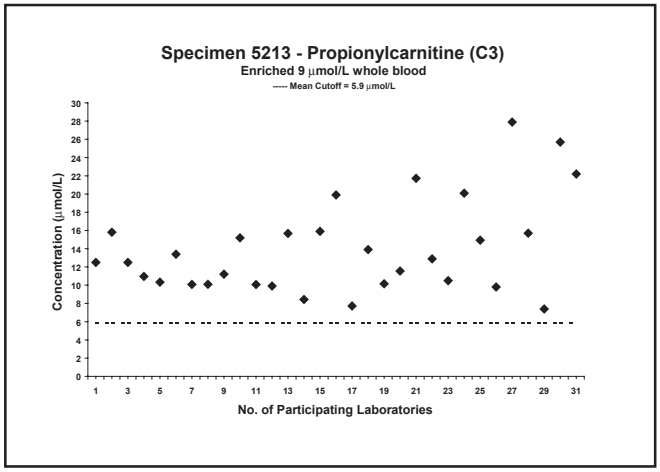

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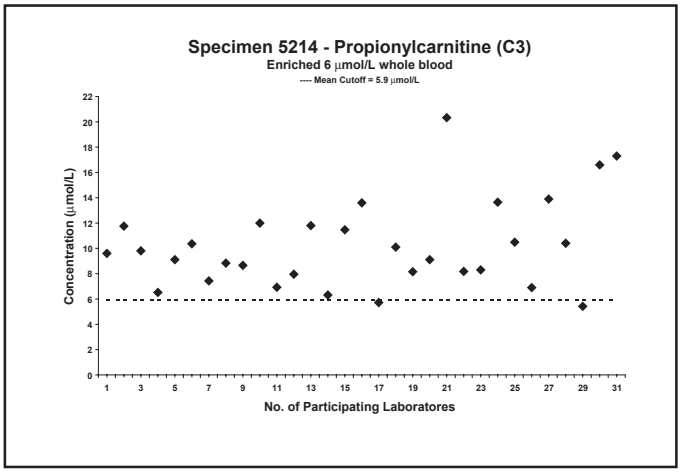

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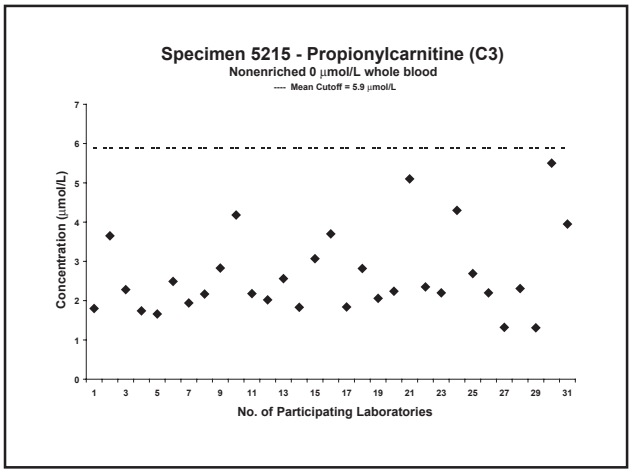
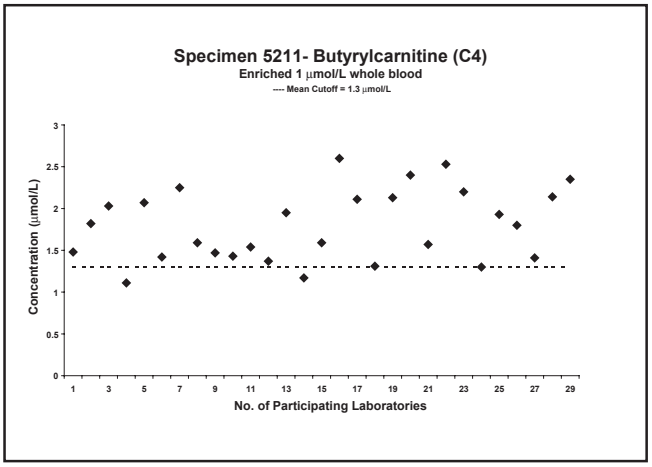


Figure 14e.

Figures 15a-15e. Participant Results vs. Reported Cutoff Mean Values for Butyrylcarnitine (C4)



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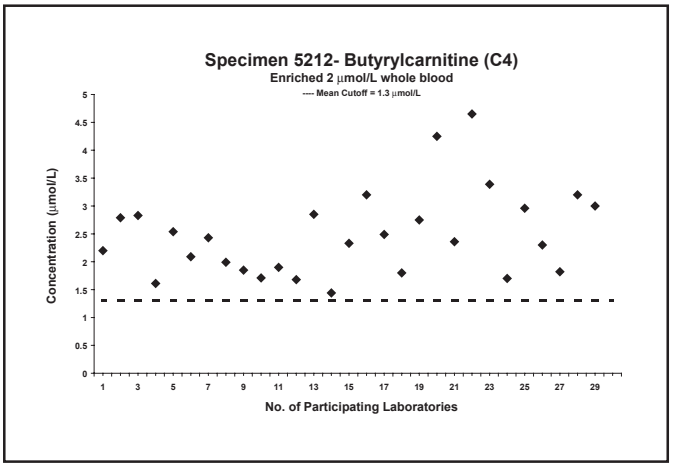

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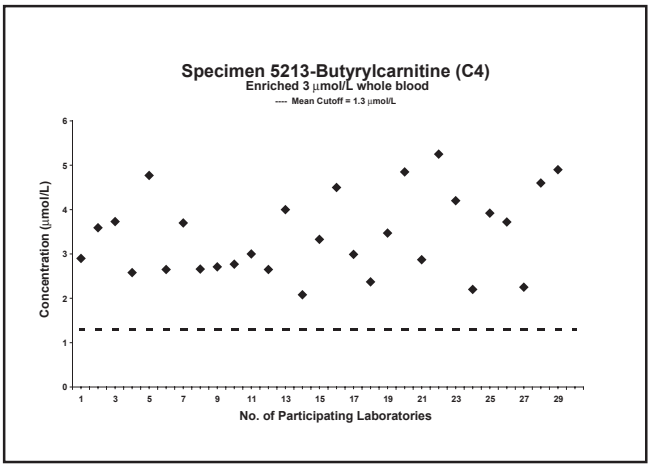

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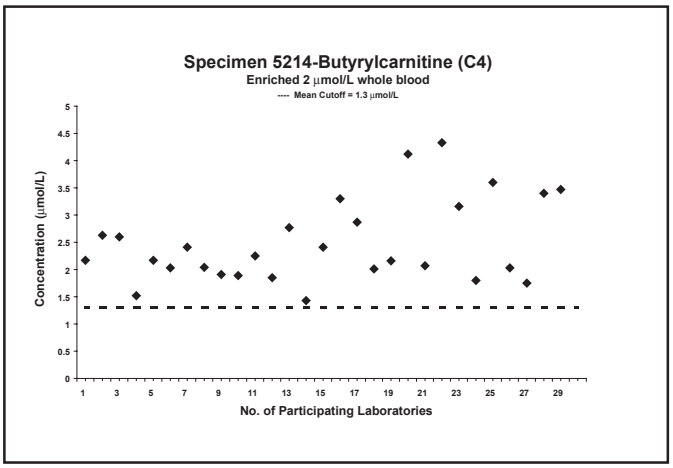

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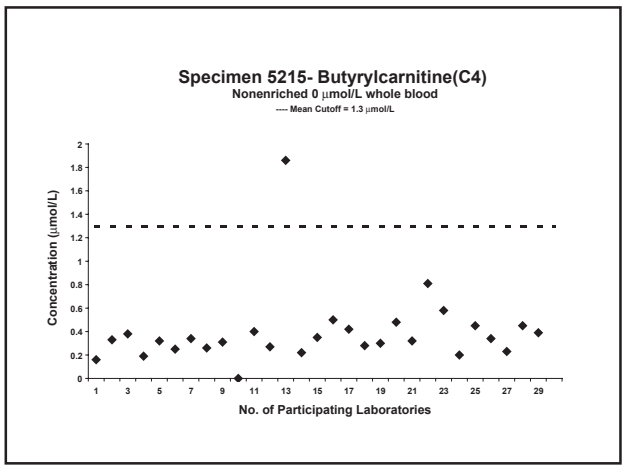
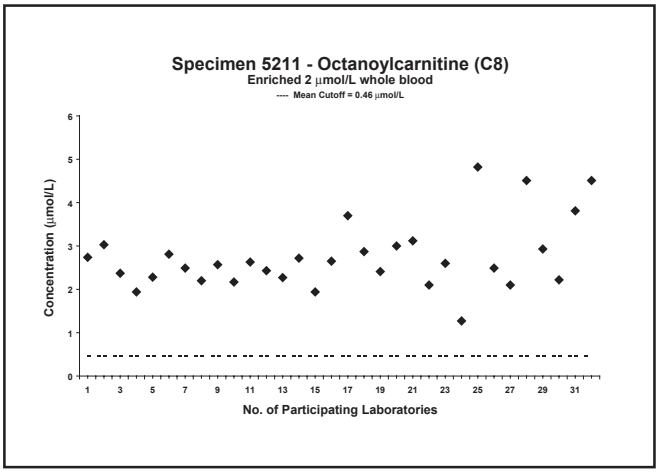


Figure 15e.

Figures 16a-16e. Participant Results vs. Reported Cutoff Mean Values for Octanoylcarnitine (C8)



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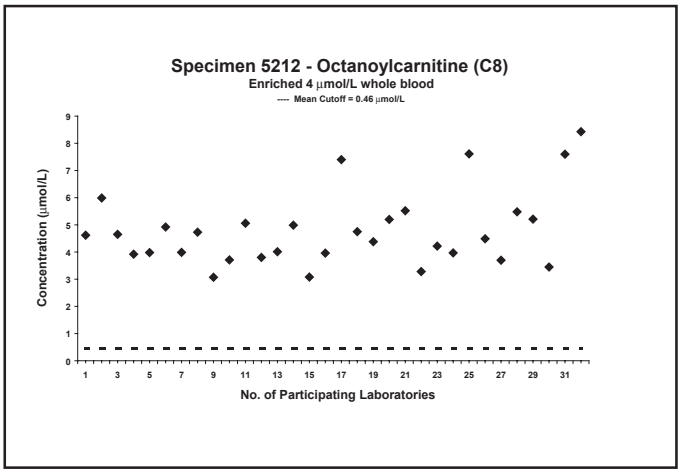

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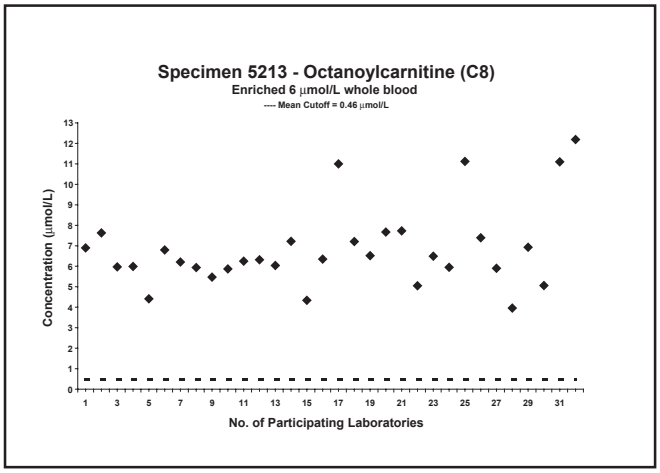

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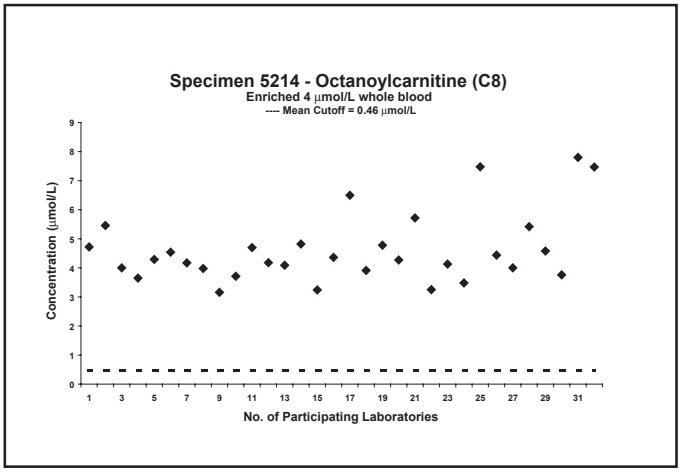

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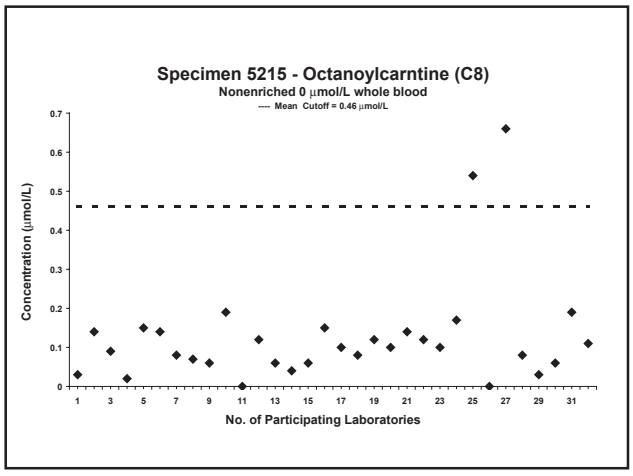


Figure 16e.

Figures 17a-17e. Participant Results vs. Reported Cutoff Mean Value for Myristoylcarnitine (C14)

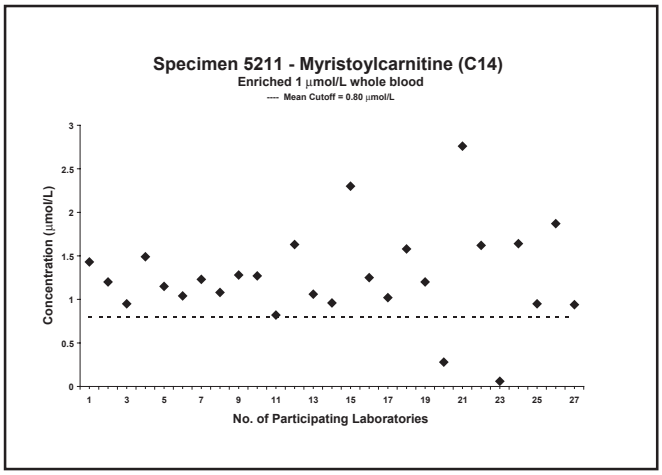
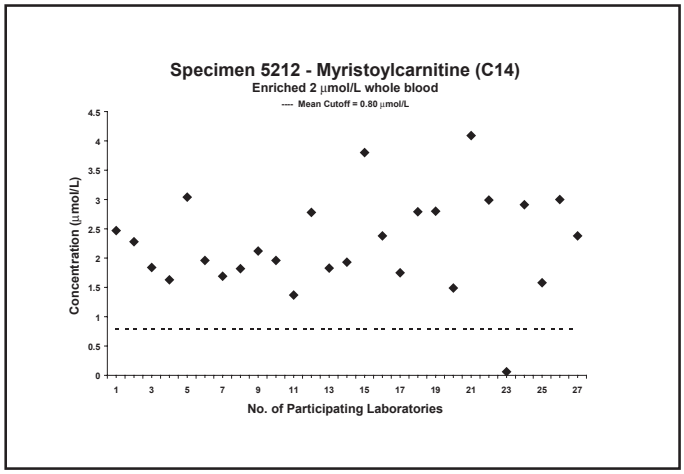


Figure 17a.



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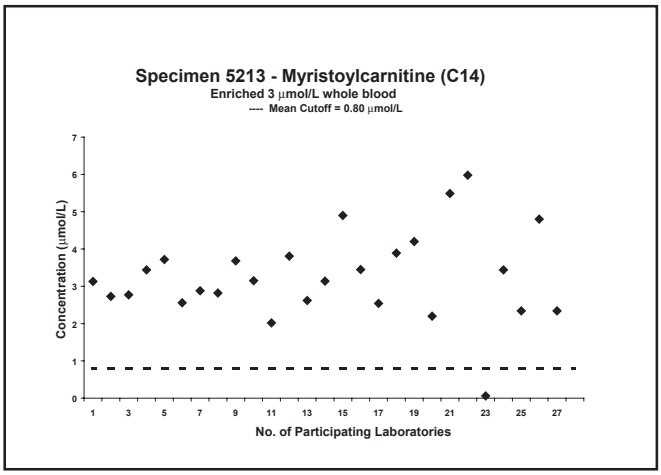

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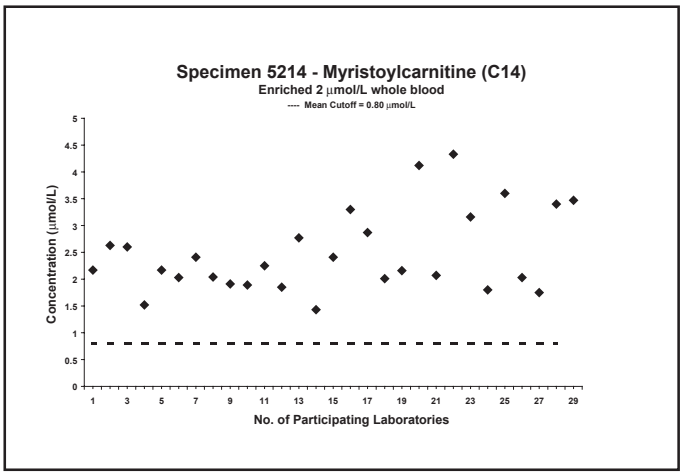

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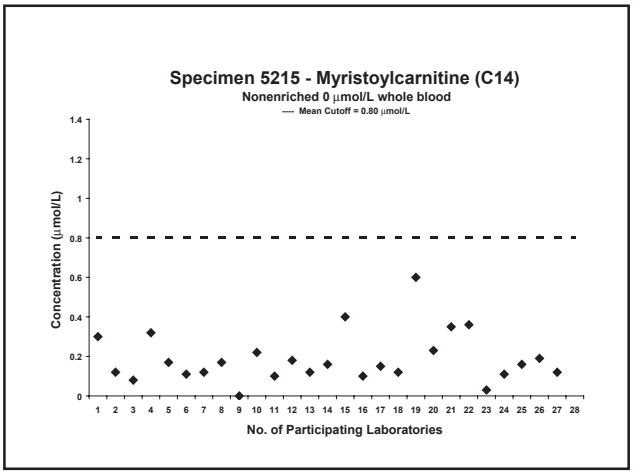
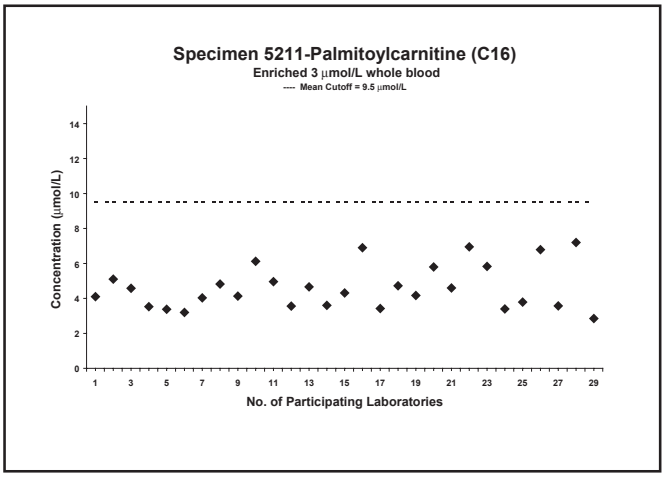


Figure 17e.

Figures 18a-18e. Participant Results vs. Reported Cutoff Mean Values for Palmitoylcarnitine (C16)



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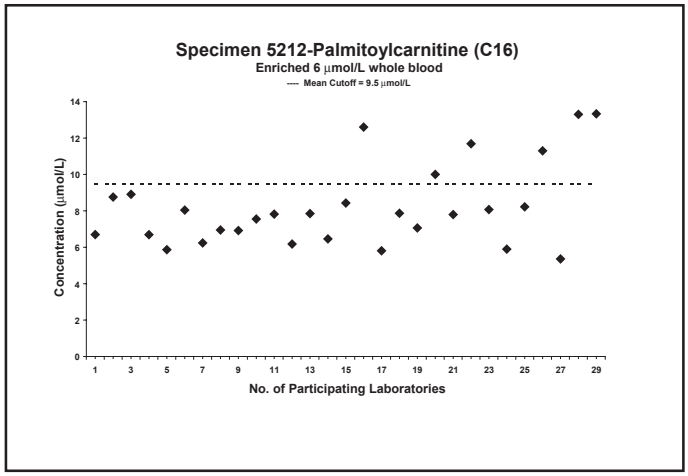

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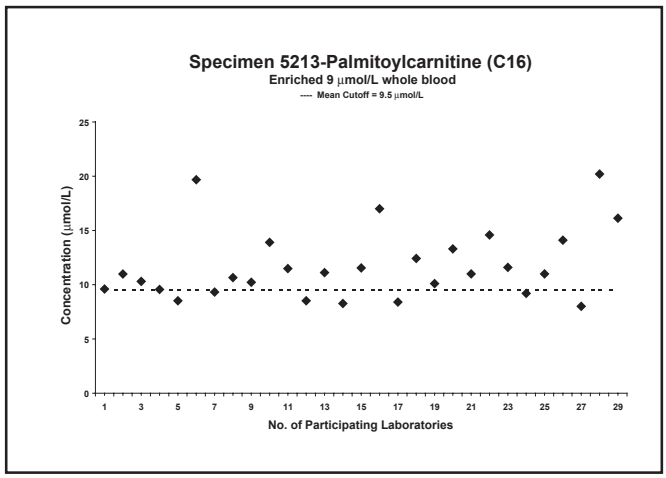

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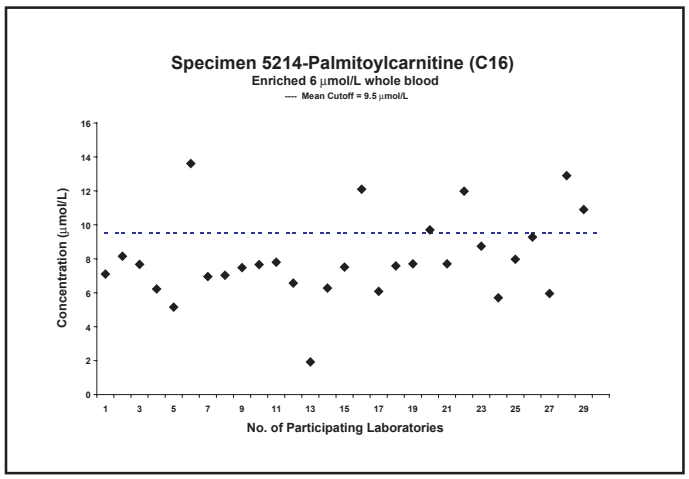

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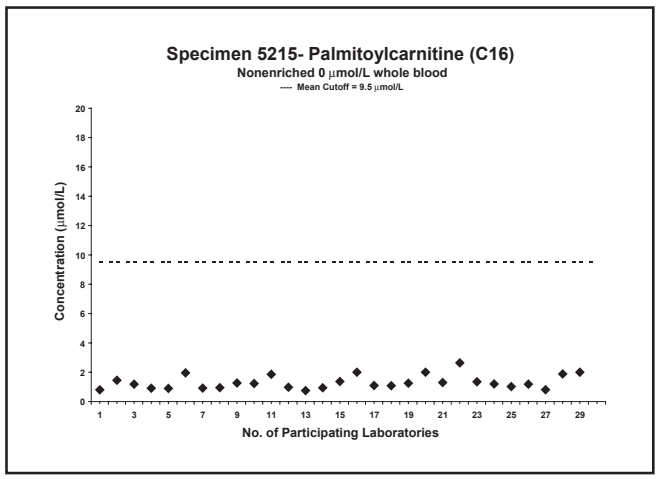

Figure 18e.

MEETINGS, WORKSHOPS, AND CONFERENCE NEWS

- The NSQAP cosponsored and helped organize the second MS/MS meeting, "Enhancing the Implementation of Tandem Mass Spectrometry for Newborn Screening Laboratories," held on September 10-11, 2001, in Madison, Wisconsin. This meeting was designed to

  (1) bring together a core discussion group of laboratory and medical scientists with a vested interest in successful newborn screening and with differing levels of expertise and experience using MS/MS technology and

  (2) address solutions to problems encountered with implementation of MS/MS testing. The meeting of approximately 200 participants was successful. Conference proceedings will be published in 2002.

- In 2001, APHL organized a subcommittee of the Newborn Screening and Genetics in Public Health Committee for quality assurance. One mission component of this subcommittee is to provide guidance to the NSQAP on procedures, policies, and activities for assessing the quality of laboratory testing. In January 2002, this subcommittee held its inaugural meeting in Atlanta, where the staff members of the NSQAP provided an overall review of their activities. We believe that input from this subcommittee will enhance our continuing efforts to better serve our participants.

- In January 2002, after months of programming and testing, NSQAP officially went "online" with the operation of its paperless data-reporting system whereby global participants can report quarterly PT data over the Internet. Quarterly PT reports for inborn errors of metabolism, biotinidase deficiency, and galactose-1-phosphate uridyltransferase (GALT) deficiency panels can be viewed online by participants with user-specific IDs and passwords. The summary data for each quarter are available for public view beginning in 2002 at http://www2.cdc.gov/nceh/NewbornScreening. The PT program for hemoglobinopathies and MS/MS are not online but are scheduled as future enhancements.

- In May 2002, the first two Tandem Mass Spectrometry wet workshops were held at Duke University Medical Center, Research Triangle Park, North Carolina, and the Institute of Metabolic Disease, Baylor University Medical Center, Dallas, Texas. The workshops are being cosponsored by the Health Resources and Services Administration (HRSA), CDC, APHL, and the National Newborn Screening and Genetics Resource Center (NNSGRC). These workshops will be offered each year at no cost to state public health laboratories and their affiliates that are in the startup phase of bringing MS/MS into their laboratories for newborn testing. Each class accommodates five students per week. In the late summer, two additional workshops will be held at the same locations for those individuals needing training in MS/MS interpretation as well as specific follow-up, confirmation, and long-term monitoring alternatives. For more information, please contact *Brad Therrell, PhD, Director, National Newborn Screening and Genetics Resource Center (NNSGRC), 1912 W. Anderson Lane #210, Austin, Texas 78757, Phone: 512-454-6419 Fax: 512-454-6509, Web site: http://genes-r-us.uthscsa.edu.*

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1. Centers for Disease Control and Prevention. Using tandem mass spectrometry for metabolic disease screening among newborns: a report of a work group. MMWR 2001; 50(No. RR-3): 1-34.

2. Chace DH, Adam BW, Smith SJ, Alexander JR, Hillman SL, Hannon WH. Validation of accuracy-based amino acid reference materials in dried-blood spots by tandem mass spectrometry for newborn screening assays. Clin Chem 1999; 45:1269-77.

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Notes

This ***NEWBORN SCREENING QUALITY ASSURANCE PROGRAM*** report is an internal publication distributed to program participants and selected program colleagues. The laboratory quality assurance program is a project cosponsored by the **Centers for Disease Control and Prevention (CDC) and the Association of Public Health Laboratories.**

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